**REMARKS**

The above-noted amendments to the claims and the addition of new claims 24-31 are respectfully submitted in response to the official action dated December 21, 2005, in which claims 1-23 were rejected.

Both the amended claims and the newly added claims now include the requirement of providing the patient with a medical gas administration device for a short period of time, such as up to six minutes. This limitation is clearly set forth in the specification including, for example, beginning at page 39, paragraph [0179]. Indeed, all of the claim limitations added hereto are fully supported in the specification, and no new matter is included therein.

Before reviewing the details of the rejection set forth in the September 24, 2005, official action, it is respectfully noted that the principal thrust of the present invention is quite different from that of the prior art cited hereagainst. Most particularly, the present invention is directed to a method for the use of a device which is to be used in conjunction with an atrial defibrillation device or a ventricular defibrillation device so that the patient can produce analgesia, anxiolysis and/or anterograde amnesia in conjunction with the pain and discomfort associated with the use of those devices. Most particularly, both the devices and the methods disclosed in the present specification for such use are ones which can apply a limited discontinuous amount of a medical gas, such as those specified herein, and which can be accomplished on an outpatient, self-medicating basis, without the need for the presence of a physician or nurse or other allied health professional. This can be vividly contrasted to the prior art cited hereagainst.

Claims 1-23 have been rejected as being unpatentable under 35 U.S.C. § 112, second paragraph. The Examiner contends that these claims are indefinite; that with respect to claims 1 and 17, "causing said patient to inhale" is indefinite and unclear; and as to claim 9, "providing for said patient to inhale" is said to be indefinite. However, in view of the above-noted amendments to each of these claims, and the positive recitation of the inhalation step now set forth in these claims, it is believed that at least this rejection has now been obviated.

Claims 1-5, 8-13, 16, and 23 have been rejected as being unpatentable over Hickle in view of Ujhelyi *et al.* under 35 U.S.C. § 103(a). Hickle is said to teach an apparatus for relief of pain and anxiety associated with medical procedures, disclosing a care system with a drug delivery system for delivering one or more gaseous sedative, analgesic or amnestic drugs in combination with oxygen gas, as well as an electronic controller and remote control device. The Examiner then admits that Hickle does not disclose that the medical procedure is used for easing a patient's pain from atrial or ventricular defibrillation, but Ujhelyi *et al.* is said to teach in a pain controlling device that it is known to provide an inhalable gas to a patient from atrial or ventricular defibrillation (citing col.3, ll.64-67; and col.3, ll.1-16 thereof). It is thus said to be obvious to provide the medical gas of Hickle to a patient receiving atrial defibrillation as taught by Ujhelyi *et al.* Based on the capabilities of the controller and remote control device in Hickle, it is said to be obvious that the remote information relating to atrial defibrillation, a third party can consider the information and assist in inhaling the medical gas. Based on the knowledge of a doctor, the amount of gas given a user based on individual users, the gas was said to be capable

of producing the effects immediately prior to, during and immediately after activating the atrial defibrillation device.

Turning to claim 2, Hickle is said to disclose a gas providing sedative, analgesic or amnestic drug, and it is said to be obvious to use one of the claimed gases, as one would look to select a known gas to provide these effects. Regarding claim 5, it is said to be obvious to have the atrial device be an atrial defibrillation implantable cardioverter defibrillator, as such devices are well known, and applicants have not disclosed any particular advantage or solution of any problem therefrom. This rejection is respectfully traversed in view of the above amendments and arguments and for the reasons set forth hereinafter.

Turning to the Hickle reference itself, this patent discloses a large and complex apparatus for use in hospital facilities for relieving pain and anxiety during painful or anxiety-producing "medical or surgical procedures." A fair analysis of the disclosure in Hickle reveals that the care system, such as care system 10 shown in FIG. 1, does provide for sedative, analgesic and/or amnestic drugs for a patient undergoing a medical or surgical procedure by a procedural physician. Thus, the housing 15 includes various storage compartments, including a drug delivery system 40 for delivering mixtures of one or more gaseous sedative, analgesic or amnestic drugs in combination with oxygen and/or other such drug delivery systems. The care system 10 also includes detailed microprocessor-based electronic controllers or computers within the housing so that during the continuing medical or surgical procedures themselves, the patient's vital signs can be monitored along with the patient's consciousness, comparisons can be made to safety data, and electronic controllers can

manage application of the drug continuously to the patient while monitoring the patient's vital signs.

The present invention is not directed to any such system. Indeed, no device is intended to continuously apply any medical gases to a patient during an extended medical or surgical procedure itself. To the contrary, a short predetermined finite dosage of medical gas is provided for a patient to self administer the drug specifically in connection with atrial or ventricular defibrillation so that, even if the patient is far away from a hospital or medical facility, the patient can immediately deal with the associated pain and anxiety which is necessary in connection with the application of such defibrillation devices.

In order to further demonstrate the significant patentable nature of the present claims over references such as Hickle, reference is made to an article by the applicants entitled "Nitrous Oxide Sedation Reduces Discomfort Caused by Atrial Defibrillation Shocks" or Ujhelyi *et al.*, *Pacing and Clinical Electrophysiology*, Vol. 27, pgs. 485-91 (April 2004), a copy of which is attached hereto. This article relates in part to the applicants' own efforts to investigate the potentially significant nature of the concept underlying the present invention. In the Ujhelyi *et al.* article, reference is made to clinical testing which occurred to determine the efficacy of gases such as $N_2O$ in mitigating atrial defibrillation shock-related anxiety, discomfort, and pain, as well as to evaluate patient acceptance of this treatment. Thus, patients with an implantable cardioverter/defibrillator having atrial therapies (ICT-AT) were utilized and the effect of $N_2O$-$O_2$ mixture treatment was evaluated. The results of this study demonstrate an important aspect of the significance of the present invention by establishing the impact of this method on anxiety,

discomfort, and pain. In the tests which were thus conducted, each of the patients received treatment with the $N_2O$ mixture until either the patients stopped following verbal commands or four minutes of dosing had elapsed. The atrial shock was administered unless refused by the patient. The results dramatically demonstrated that in waking patients, this specific $N_2O$ therapy significantly reduced shock-related anxiety, intensity, pain and discomfort by approximately 50-80%. The authors concluded that these results suggested that this type of $N_2O$ therapy can be a safe and effective one to mitigate anxiety, pain and discomfort associated with ICD-AT atrial shocks, particularly as compared to the prior use of commonly used sedatives which incapacitated the patients for several hours. As stated in this article, "The principal benefit of the ICD-AT device is patient controlled defibrillation therapy for episodic AF without the need of a healthcare professional or facility." The subject matter of the claims of the present invention have, of course, now taken this conceptual data one step further, and actually demonstrated that this is truly the case. Compared to the system described in the Hickle reference, which is clearly limited to bedside use in a hospital, clinic or doctor's office, requiring the involvement of a medical professional, and which is not applicable to providing the benefits of the present invention, it is once again clear that the presently claimed invention provides a significant step forward in the art.

Applicants would next note that the Examiner has also applied these references to claim 9 and the claims dependent thereon. However, there is no reference whatsoever to ventricular defibrillation in this prior art. Indeed, ventricular fibrillation is a totally random event, in which the present invention now makes it possible to have the required analgesic, anxiolytic or anterograde amnesia agent available to

the patient at any place and time for self medication immediately after the shock from the implantable cardioverter defibrillator or ICD device. The prior art provides no suggestion whatsoever of such a method.

Applicants would again emphasize, in connection with all of the claims pending in this application, that use of a predetermined short dosage (*i.e.* up to six minutes) device of the present invention, particularly as compared to the continuous flow of gases or other drugs in connection with Hickle, provides dramatically significant improvements in the results obtainable by patients utilizing this method.

The Examiner, admitting the deficiencies of Hickle, has combined this reference with Uljelyi *et al.* This reference, of course, is quite familiar to applicants, including Uljelyi himself, a co-inventor of the present invention. The Examiner has cited this reference for its disclosure of a pain-controlling device for provision of an inhalable gas, allegedly in connection with atrial or ventricular defibrillation procedures. Turning to Ujhelyi *et al.* itself, however, it is initially noted that this entire reference is specifically directed to a patient pain management system in which direct communication is obtained between an implanted device and an external drug delivery system so that, upon an arrhythmia condition, an alert will be provided which is communicated to the external drug delivery arrangement. Thereafter, the implanted medical device receives a communication when the drug has been administered, and only then can defibrillation proceed. It is therefore initially noted that, even in connection with atrial defibrillation, there is no reference whatsoever in this prior art to remotely communicating information relating to activation of the atrial defibrillation

device before consideration by a remotely located third party, as required by claim 1 herein. Indeed, there is no reference whatsoever to the overall thrust of the present invention relating to remotely administering this procedure in the first instance.

Secondly, with respect to ventricular defibrillation, although it is mentioned once in Ujhelyi *et al.*, it is clear that the overall thrust of this patent is specifically directed to atrial defibrillation. Indeed, the overall system disclosed in Ujhelyi *et al.* requires two-way communication between the implanted medical device and the external drug delivery arrangement for initial administration of the drug, further communication between these devices, and finally permission for the implanted medical device to deliver the electrical therapy thereof. None of this, of course, can possibly relate to the ventricular defibrillation to which claim 9, for example, is directed. This is clearly the case since ventricular defibrillation is a totally random event, and one in which sedation, for example, must be available to the patient for self medication immediately <u>after</u> the shock from the device. This clearly eliminates the possibility of using a device such as that described in Ujhelyi *et al.* under such circumstances. It is therefore respectfully submitted, aside from the fact that there is no clear teaching in either of these references to make the combination which the Examiner has effected, that even with this combination the specifically claimed methods of the present invention are nowhere taught or suggested thereby.

As it is believed that all of the rejections set forth in the Official Action have now been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone applicant's attorney at (908) 654-5000 in order to overcome any additional objections which the Examiner may believe to remain appropriate in this case.

Finally, if there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: March 20, 2006

Respectfully submitted,

By ______

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# Nitrous Oxide Sedation Reduces Discomfort Caused by Atrial Defibrillation Shocks

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**UJHELYI, M., ET AL.: Nitrous Oxide Sedation Reduces Discomfort Caused by Atrial Defibrillation Shocks.** *An implantable cardioverter defibrillator with atrial therapies (ICD-ATs) is an effective therapy to manage atrial tacharrhythmias. Acceptance of this therapy is limited by atrial shock related anxiety and discomfort. Inhaled nitrous oxide ($N_2O$) is a potent sedative-analgesic-anxiolytic agent that may mitigate shock discomfort and anxiety and improve patient ICD-AT acceptance. ICD-AT patients with more than one ambulatory atrial shock within 12 months were enrolled and grouped by ICD-AT shock method; awake ($n = 9$) or asleep ($n = 4$) when ambulatory ICD-AT shock is delivered. A baseline questionnaire assessed the most recent ambulatory ICD-AT shock ($3 \pm 3$ months). A 65% $N_2O$/35% $O_2$ mixture was inhaled for 4 minutes followed by an ICD-AT test shock ($18 \pm 8$ J). The test shock mimicked the awake shock method. The test shock experience during $N_2O$ was evaluated via questionnaire immediately following and 24 hours after the shock. Shock related anxiety, intensity, pain, and discomfort were assessed using a ten-point rank scale. Baseline test shock scores were similar between the shock method groups. In the awake shock method group, $N_2O$ greatly reduced preshock anxiety by 48% ($6.4 \pm 2.4$ to $3.3 \pm 2.0$, or), and shock related intensity ($5.9 \pm 3.1$ to $3.3 \pm 2.5$), pain ($5.0 \pm 2.6$ to $2.0 \pm 2.1$), and discomfort ($5.6 \pm 2.4$ to $1.3 \pm 1.4$) from baseline values by 45%, 60%, and 78% ($P < 0.05$), respectively. The asleep shock method group reported no changes in shock related anxiety, intensity, pain, or discomfort. Atrial shock concern, assessed via a five-point rank scale (5 = extreme concern) was improved by $N_2O$ but only in the awake group ($3.1 \pm 1.0$ baseline to $1.6 \pm 0.5$ $N_2O$, $P = 0.008$). There were no adverse events with $N_2O$ and patients fully recovered within 5 minutes after $N_2O$. In conclusion, 65% $N_2O$ greatly reduced shock related pain and discomfort, and significantly reduced atrial shock concern but only in the awake shock method group. The benefits of $N_2O$ therapy may expand the use and acceptability of ICD-AT therapy into a larger atrial fibrillation cohort. (PACE 2004; 27:485–491)*

***defibrillation, pain, analgesia, sedation, atrial fibrillation***

## Introduction

The growing numbers of refractory atrial tachyarrhythmia (AF) patients have produced new therapeutic approaches. One such approach is the implantable cardioverter defibrillator that has atrial therapies (ICD-AT). The atrial therapies are atrial overdrive pacing, atrial antitachycardia pacing, and atrial defibrillation therapy. The ICD-AT has undergone clinical trials and has received market approval for the "AF Only" indication (no evidence of ventricular tachycardia/fibrillation [VT/VF]) in drug refractory AF patients.[1] The principal benefit of an ICD-AT device is patient-controlled defibrillation therapy for episodic AF without the need of a health care professional or facility.[1] The limitation to this therapy is shock induced patient discomfort.

Defibrillation pain and discomfort comprises a sensory and affective component. The affective pain component of defibrillation discomfort is evidenced by patients perceiving a second defibrillation shock as more painful/discomforting than a preceding shock of equal or lower energy. As the number of shocks increase, the patient is less likely to tolerate the shock and more likely to require sedation therapy.[2–4] These findings are consistent with brain magnetic resonance imaging data that demonstrate pain anticipation is a confounding variable that may heighten pain perception.[5] Hence, pain anticipation and fear heightens the overall pain and discomfort perception, and contributes to decreased patient tolerance over time. Therefore, anxiolytic therapy, like short acting oral benzodiazepine drugs or inhaled nitrous oxide ($N_2O$), might be able to provide considerable relief of atrial shock discomfort. $N_2O$ has ideal properties for this purpose including (1) rapid onset (peak effect within minutes), (2) rapid offset (duration of action <5 minutes), (3) rapid dose titration, and (4) relative safety with minimal respiratory and cardiovascular depression.[6] $N_2O$ is

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a strong analgesic and weak anesthetic agent and can decrease fear and anxiety. These properties suggest that $N_2O$ may be an attractive therapy to relieve the pain/discomfort associated with atrial defibrillation.

There are no data reporting $N_2O$ safety and efficacy in mitigating defibrillation shock discomfort. The primary objective of this trial was to generate pilot data regarding $N_2O$ efficacy in mitigating atrial defibrillation shock related anxiety, discomfort, and pain. The secondary objectives were to evaluate patient acceptance of $N_2O$ sedation and $N_2O$ safety.

## Methods

This single center study recruited 13 patients with implanted Jewel AF or Gem III AT (Models 7250 and 7276, respectively, Medtronic Inc., Minneapolis, MN, USA) arrhythmia management devices. All patients had AF as the primary device indication, rather than a ventricular arrhythmia indication. Eligible patients were at least ≥1 month from device implant date and had experienced at least one atrial defibrillation shock within the last 12 months while fully conscious in an ambulatory setting. The local Institutional Review Board approved this trial and all patients provided written, informed consent to receive an atrial defibrillation shock while in normal sinus rhythm or during an ongoing atrial arrhythmia for the sole purpose of rating atrial defibrillation shock discomfort.

Patients were grouped according to the their typical method of "out of clinic" ambulatory atrial shock. One group received an ambulatory shock via the ICD-AT device while awake (awake group) while another group of patients received the atrial shock during sleep (asleep group). While both shock method groups were included, the test shock for this protocol mimics the awake shock method (atrial shock delivery while awake in the middle of the day). The following exclusion criteria ensured patient safety: severe pulmonary dysfunction, home oxygen ($O_2$) dependent, benzodiazepine use within the last 12 hours, known unacceptable side-effects during prior $N_2O$ experience, New York Heart Association (NYHA) Class III or IV heart failure, systolic blood pressure <90 mmHg, ventricular heart rate >130 beats/min, concurrent anxiety disorder (DSM IV classified), contraindications to $N_2O$ usage, and pregnancy. For data collection purposes, patients who were unable to accurately recall or articulate their most recent atrial shock experience were also excluded.

The study was open label and all patients received active treatment with a gaseous mixture of 65% vol $N_2O$ plus 35% vol $O_2$. Patients received an atrial shock during normal sinus rhythm or for a hemodynamically stable atrial arrhythmia. Patients presented to the clinic for study evaluation after fasting for >4 hours. During the evaluation, patients had a physical examination, medication review, atrial shock history review via device interrogation, and completed a baseline shock discomfort questionnaire. Patients completed the baseline shock discomfort questionnaire approximately 1 hour before the study procedures. This questionnaire assessed the patients' most recent fully conscious atrial defibrillation therapy experience.

Subsequently, patients were placed in a comfortable reclining chair or bed. Procedure preparation included placement of a continuous pulse oximetry-monitoring probe on the digit or ear lobe, placement of an automated blood pressure cuff around the upper arm, and continuous electrocardiographic (ECG) monitoring. Patients were instructed on how to self-administer the $N_2O$ mixture (with medical supervision). $N_2O$ was administered using a hand held face mask and a demand valve regulator (model # 91120507, MDS Matrx, Orchard Park, NY, USA). After the patient understood the procedures and responsibilities, the patient held the face mask firmly over their mouth and nose and $N_2O$ therapy was delivered with each breath. During $N_2O$ therapy, pulse oximetry and vital signs (ECG rhythm, heart rate, blood pressure, and respiration rate) were recorded every 30–60 seconds. Patients were also asked to follow a simple verbal command to assess cognition level and responsiveness.

Each patient received the $N_2O$ mixture until one of two scenarios occurred: (1) the patient stopped following verbal commands, or (2) the patient had received 4 minutes $N_2O$ dosing. No patient experienced an adverse event requiring discontinuation of $N_2O$ treatment. The physician or his designee administered an atrial shock unless the patient refused the atrial shock, particularly if he/she did not feel adequately sedated. The atrial shock was delivered via an external programmer device (Model 9790, Medtronic) and the defibrillation energy and pathway was individualized for each patient (i.e., equal to the baseline-indexed atrial shock).

After the patient received the shock, he/she was queried every minute to report the return of normal sensorium. Once the patient's self-reported mental acuity returned to baseline, he/she completed the shock experience questionnaire that assessed shock related pain/discomfort, $N_2O$ response, and willingness to use $N_2O$ for the next atrial defibrillation therapy. Approximately 24 hours after receiving the shock, the patient completed a third shock experience questionnaire to ascertain short-term memory of the shock experience during $N_2O$.

## Data Collection

Atrial shock perception was assessed via visual rank scale. These data were collected at baseline, immediately after test shock (10–15 minutes) and then 24 hours after test shock. Patients were specifically asked to rate the severity of anxiety just prior to an atrial shock, shock intensity, shock related discomfort, and shock related pain. Each question used a rank scale from 0 to 10, where 0 represented none and 10 represented severe anxiety, intensity, discomfort, or pain. Patients were also asked about shock related concern. The patients were ask to describe how much concern they have regarding shock discomfort the next time an atrial defibrillation therapy is required. Patient response ranged from no concern, some concern, moderate concern, very concerned, and extremely concerned it is always on my mind. These answers were scored from 1 to 5, respectively. Shock concern evaluates shock acceptance, whereby patients who have very or extreme concern do not accept atrial shock therapy.[7]

$N_2O$ therapy effects were assessed to determine patient reported side-effects and patient acceptance. Each question used a rank scale from 0 to 10, with 0 representing no affect and 10 representing extreme effect. Patients were also asked to rank the extent to which $N_2O$ was a pleasant experience and how $N_2O$ affected willingness to use $N_2O$ for future atrial shocks. Scores were ranked on a 0–10 scale where 0 represented a negative response (i.e., very unpleasant or very unwilling) and 10 was a positive response (i.e., very pleasant or very willing).

## Data Analysis

The primary outcome was the absolute change between baseline and the 24-hour survey response within a patient group. Comparisons within the group were analyzed with a two-way ANOVA. Post hoc analysis for significant differences was determined using the Tukey test. Comparisons between groups were made using the Student's *t*-test. In all cases, the data were tested for normal distribution and equal variances. When these assumptions failed, the appropriate nonparametric test was substituted.

## Results

Baseline ambulatory atrial defibrillation therapy mode was awake method in nine patients and asleep method in four patients. Eight patients in the awake group activated ambulatory atrial shocks via an external patient activator device while one patient used automatic programmed therapy while awake timed to 10 PM. The asleep group patients used automatic programmed therapy timed to sleep (1–5 AM). Table I reports patient demographics according to shock method group. There were no statistical differences between groups, however, the asleep shock method group tended to have higher body weight and atrial shock energy. Most patients (n = 9) were ≤1 year from ICD-AT implantation. ICD-AT data logs demonstrated that patients had received an average of 0.9 ± 1 atrial defibrillations per month within the last year. The median interval between the study day and the patient's most recent ICD-AT atrial shock was 3 months, with the most recent ICD-AT shock occurring on the $N_2O$ study day, and the most distant ICD-AT shock occurring 10.5 months before the $N_2O$ study day. Nine patients received the investigational shock during normal sinus rhythm, and four patients received it during an AF episode. The four AF patients did not accept ambulatory atrial shocks and presented to the clinic to receive intravenous sedation. This was evidenced by the AF patients reporting greater ($P < 0.05$) baseline shock related intensity (9.0 ± 4.6 vs 5.0 ± 2.7), pain (8.0 ± 2.8 vs 4.9 ± 2.2), and discomfort (8.3 ± 2.1 vs 5.0 ± 2.3) versus normal sinus rhythm patients, respectively.

**Table I.**

Patient Demographics

| | Awake Method Group (n = 9) | Asleep Method Group (n = 4) |
|---|---|---|
| Age (years) | 68 ± 11 | 66 ± 9 |
| Sex (% male) | 78% | 75% |
| Weight (pounds) | 211 ± 30 | 287 ± 83 |
| Implant Duration (year) | 1.0 ± 1.0 | 0.9 ± 1.3 |
| Atrial Energy | 17 ± 8 | 22 ± 8 |
| Most recent ambulatory atrial shock (months) | 3.4 ± 3.1 | 3.0 ± 5.0 |
| # Atrial shocks in last year | 6 ± 5 | 5 ± 5 |
| Rhythm status: NSR vs AF | 6 vs 3 | 3 vs 1 |
| Previous $N_2O$ use in last 5 years (%) | 33% | 0% |

AF = atrial fibrillation; NSR = normal sinus rhythm; $N_2O$ = nitrous oxide.

As mentioned above, no patient stopped $N_2O$ therapy because of intolerant adverse effects. However, three patients terminated $N_2O$ therapy prematurely and received the test shock early because they stopped following verbal commands. All three patients were in the awake group, which resulted in a shorter $N_2O$ therapy duration in the awake versus asleep group ($P = 0.07$). However, none of these patients ever lost consciousness. One

patient in the awake group refused the atrial shock. This patient typically received intravenous midazolam for each ICD-AT atrial shock. $N_2O$ was unable to yield a sufficient level of sedation for this patient.

Figures 1 and 2 report individual patient and mean ± SD data for all shock evaluation scores at each evaluation period. The patient who refused the test shock was removed from analysis since she had no test shock scores. There were no baseline differences between shock modes for all metrics. Response to $N_2O$ therapy was noticeably different between groups. The sleep method group had no response to $N_2O$ therapy such that shock scores were similar between baseline and $N_2O$ study phases. In the awake shock method group, $N_2O$ significantly reduced preshock anxiety, shock related intensity, pain, and discomfort scores from baseline to the 24-hour evaluation time point by 48%, 45%, 60%, and 78% ($P < 0.05$), respectively. Individual point response in the asleep group show no trends and apparently random changes between evaluation phases. However, individual responses in the awake group show the majority of patients reporting lower scores, although a few patients had no or increased discomfort scores. The three patients who stopped following verbal commands during $N_2O$ therapy (the highest sedation level) reported the greatest reduction in shock scores.

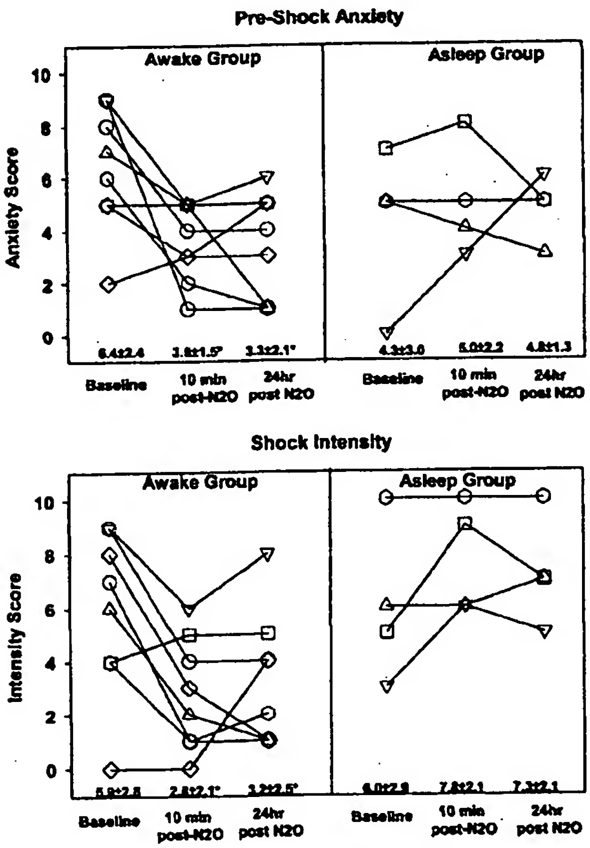


**Figure 1.** *Patient evaluation of preshock anxiety (top panel) and shock intensity (bottom panel) at baseline, 10 minutes after shock delivery, and 24 hours after shock delivery. Line graph represents individual patient response on a 0–10-point scale and numbers represent mean ± SD for each evaluation phase. The asterisk represents P < 0.05 versus baseline.*

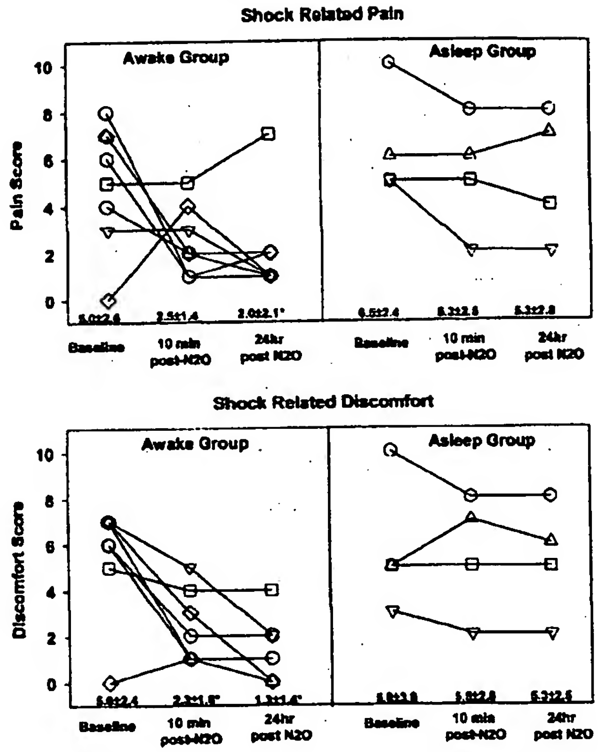


**Figure 2.** *Patient evaluation of shock pain (top panel) and shock discomfort (bottom panel) at baseline, 10 minutes after shock delivery, and 24 hours after shock delivery. Line graph represents individual patient response on a 0–10-point scale and numbers represent mean ± SD for each evaluation phase. The asterisk represents P < 0.05 versus baseline.*

The reduction in shock perception scores was associated with a reduction in shock concern. The awake patient group reported that $N_2O$ reduced their concern about atrial shock discomfort from 3.1 ± 1.0 to 1.6 ± 0.5 ($P = 0.008$) where 5 equals extreme concern. In the asleep group, atrial shock concern scores were unaffected by $N_2O$ (2.5 ± 1.0 vs 2.3 ± 1.0).

Patient reported assessment of $N_2O$ therapy is listed in Table II. Patients overall rated the $N_2O$ experience as pleasant with no reported adverse

**Table II.**

$N_2O$ Effects

| Patient Reported Effects While Breathing $N_2O$ | Awake Method Group (n = 9) | Asleep Method Group (n = 4) |
|---|---|---|
| Anxiety (0 = none; 10 = severe) | 3.1 ± 2.3 | 4.5 ± 2.6 |
| Dizziness (0 = none; 10 = severe) | 3.3 ± 3.2 | 3.0 ± 3.6 |
| Nausea (0 = none; 10 = severe) | 0.5 ± 0.7 | 1.0 ± 2.0 |
| Sleepiness (0 = none; 10 = severe) | 5.7 ± 2.9 | 3.3 ± 3.3 |
| Difficulty following verbal commands (0 = none; 10 = severe) | 3.6 ± 1.0 | 1.0 ± 2.0 |
| $N_2O$ Pleasantness (0 = unpleasant; 10 = very pleasant) | 8.1 ± 2.0 | 7.5 ± 2.1 |
| Willingness to use $N_2O$ again (0 = unwilling; 10 = very willing) | 8.0 ± 3.8 | 7.0 ± 3.6 |

(0 = none; 10 = severe). $N_2O$ = nitrous oxide.

events. While there were no statistically significant differences between shock groups, these data corroborate the primary finding that the awake group achieved a greater level of $N_2O$ sedation than the asleep group. The awake group showed a trend towards greater sleepiness and difficulty following commands with less anxiety. However, both groups indicated a high willingness to use $N_2O$ therapy for their next atrial shock.

There were no adverse events reported before, during, or after $N_2O$ therapy. All patients tolerated $N_2O$ therapy and no patients discontinued dosing because of intolerability. Figure 3 shows no significant changes in respiration rate before, during, and after $N_2O$ therapy. As anticipated, patients breathing a 35% vol oxygen mixture produced a significant increase in oxygen saturation from the 2- to 4-minute time period ($P < 0.05$). $N_2O$ therapy produced no meaningful effect on pulse or blood pressure during $N_2O$ therapy (Fig. 4). All patients recovered from $N_2O$ effects within 3–4 minutes of discontinuation, and reported that cognition and central nervous system function returned to baseline.

## Discussion

ICD-AT patients average one atrial defibrillation shock per patient month.[1,8] When ICD-AT shock frequency is low, most patients tolerate therapy without needing intravenous or oral sedation.[9] Increased atrial shock frequency is a clear predictor of shock intolerance and need for sedation.[3] However, all commonly used sedatives incapacitate patients for several hours, adversely affecting patient acceptance of sedation and ICD-AT therapy. The goal of this study was to determine if the rapidly acting sedative/analgesic agent $N_2O$ could mitigate shock related pain/discomfort, and hence improve atrial shock acceptance. Since $N_2O$ has a very rapid onset and offset of action, patients and physicians are likely to accept this sedation modality if it has clinical benefit. The data from this study demonstrated that $N_2O$ therapy significantly reduced shock related anxiety, intensity, pain, and discomfort by approximately 50–80%, but only in the awake shock method group. Interestingly, patients who typically receive atrial shocks automatically while asleep did not report any benefit from $N_2O$ therapy. The reduction in atrial shock scores in the awake group was associated with greater $N_2O$ sedation and a reduction in atrial shock concern. Overall, these preliminary data suggest that $N_2O$ may be a safe and effective therapy to mitigate anxiety, pain, and discomfort associated with

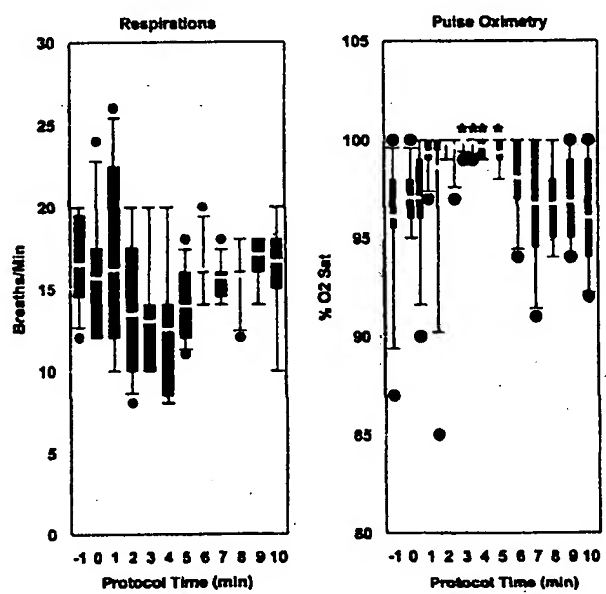


**Figure 3.** *Box plots of respiration rate (left panel) and oxygen saturation (right panel) over the study duration. $N_2O$ began at time = 0 and ended at time = 4 minutes. The solid bars represent the 25th to 75th percentile and the whiskers represent the 10th to 90th percentile and the circles represents outliers. The white line within the solid bars represents the mean value. The asterisk represents $P < 0.05$ versus time = 0.*

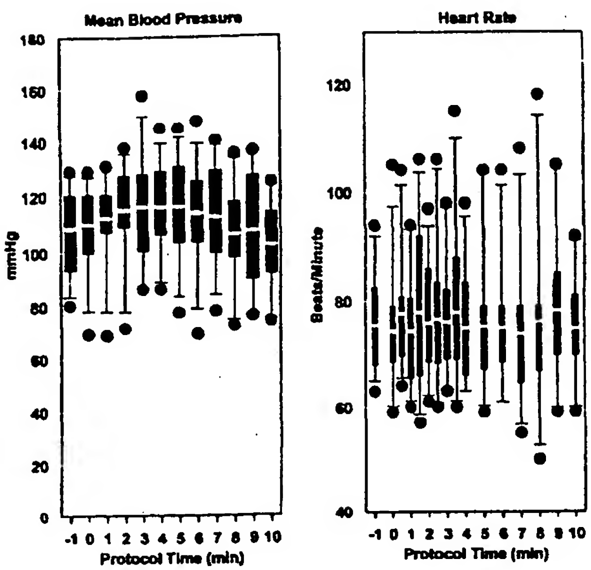


**Figure 4.** *Box plots of mean blood pressure (left panel) and heart rate (right panel) over the study duration. $N_2O$ began at time = 0 and ended at time = 4 minutes. The solid bars represent the 25th to 75th percentile and the whiskers represent the 10th to 90th percentile and the circles represents outliers. The white line within the solid bars represents the mean value.*

ICD-AT atrial shocks, particularly for patients who routinely receive awake atrial shocks.

It was expected that a potent sedative like $N_2O$ would reduce atrial shock related anxiety, pain, and discomfort. However, it was somewhat surprising that this effect was only observed in the awake shock method group. There are two possible explanations for this observation. First, the sleep method group was challenged to compare an automatic sleep shock (i.e., baseline) to a daytime manual awake shock (i.e., test shock). Since automatic atrial defibrillation therapy during sleep may be better tolerated than awake shocks, there is bias towards higher anxiety/pain/discomfort scores with the awake shock regardless of $N_2O$ therapy.[7,10,11] Second, it is possible that changing the shock mode to an unfamiliar delivery method, asleep to awake mode as required by protocol, could heightening preshock anxiety and hence pain and discomfort. Therefore, it is possible that delivering the test shock via the awake method could have offset any $N_2O$ benefit in the asleep shock mode patients. It is also possible that there is a type II statistical error given the small number of patients in the sleep method group and that a larger sample size would show some benefit.

A placebo or control group was not included in this study. It is recognized that a placebo effect could be responsible for the positive findings. However, the asleep group did not respond to $N_2O$ therapy suggesting little or no placebo effect in this patient cohort. Moreover, it is very unlikely that a placebo effect would cause patients to abruptly halt following verbal commands. However, this is an expected $N_2O$ effect. Lastly, it is unlikely that a placebo response would elicit a 50–80% reduction in discomfort/pain scores. Overall, these data indicate that $N_2O$ and not placebo are responsible for the current findings. Fortunately, an ongoing placebo-controlled trial has demonstrated that patient reported historical shock scores are equivalent to placebo reported shock scores (personal communications Patricia Krobroth, Ph.D, University of Pittsburgh). In this study, patients used the identical rating scale as the current study, and compared a baseline distant shock experience (months after shock) with an acute shock experience (12 hours after the shock) during double-blind placebo therapy. Hence, the totality of evidence indicates that $N_2O$, rather than placebo is responsible for the current findings.

The goal of this study was to improve shock acceptance by reducing shock pain and discomfort. Shock acceptance is a broad construct based on the psychological accommodation of the pros and cons of the shock and the derivation of benefit from the shock in terms of biomedical, psychological, and social functioning. Previous data show that shock concern is a good proxy for shock acceptance.[7] In the current study, $N_2O$ therapy improved shock concern significantly but only in the awake group. Patients who entered the study with an AF episode recurrence had the highest shock concern. In all cases, the AF patients were seeking intravenous sedation therapy but agreed to try $N_2O$ therapy and enrolled into the current study. These patients had significantly higher baseline pain/discomfort scores, again indicating poor shock acceptance. Nevertheless, two of the four AF patients had >60% reduction in pain and discomfort with $N_2O$ therapy, and only one patient refused the shock. These data suggest $N_2O$ therapy improves atrial shock acceptance in an unaccepting patient population.

The 4-minute dose duration in the current study was chosen to achieve rapid recovery and minimize disruption in a patient's daily routine. In this regard, no patient lost consciousness during $N_2O$ therapy, and all patients were fully recovered to baseline mental status within 3–5 minutes following $N_2O$ therapy. These data are consistent with cognitive and motor function studies that demonstrate patients are fit to drive an automobile within 15 minutes of $N_2O$ therapy cessation.[12]

There are numerous strategies to reduce atrial shock associated pain/discomfort. Neither energy

reduction nor waveform modifications are associated with lower pain/discomfort scores.[2,11] Rather, low energy levels (i.e., 0.5 J) can be extremely painful and are rated similar in pain intensity to shocks fourfold higher in energy.[13] However, a few reports indicate that atrial defibrillation therapy delivered during sleep may somewhat improve shock acceptance.[7,10,11] This is logical since sleep is a natural sedate state with minimal anxiety, and suggests that sedation and not analgesia is the target outcome of discomfort-mitigating therapy. Experience with narcotic analgesic treatment support the supposition that preshock anxiety is an important variable affecting shock acceptance, since intranasal butorphanol does not reduce shock related pain/discomfort relief.[4] Intravenous or oral sedation therapy effectively reduces shock related pain/discomfort. Indeed, several patients in the current study (n = 4) relied on intravenous midazolam therapy to accept atrial defibrillation therapy. Oral benzodiazepines are generally safe for ambulatory use but have limited effectiveness reducing shock pain/discomfort. For example, oral midazolam (15 mg) modestly reduced ICD-AT associated baseline pain and unpleasantness by 25% while not affecting anxiety.[14] In the current study, $N_2O$ therapy reduced shock related pain/discomfort by a greater magnitude than oral sedation but is less effective than intravenous sedation.[15] However, patients who achieved a high sedation level reported shock related pain/discomfort scores in a range similar to intravenous sedatives, suggesting that ambulatory $N_2O$ treatment could be an acceptable alternative to institutionally based intravenous sedation.[3]

### Clinical Implications

The constellation of shock related anxiety, pain, and discomfort limits shock frequency and hence may undermine ICD-AT therapeutic use. Methods to increase shock acceptance are likely to lead to improved atrial rhythm control, reduction in AF symptoms, and perhaps improved hemodynamic function. The current study indicates that $N_2O$ may be a convenient and safe method to reduce shock associated pain and discomfort. $N_2O$ improved shock acceptance, and patients readily accepted the rapid onset of action and recovery time that minimized the impact of ICD-AT shocks on daily activities.

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